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09/889,267	01/17/2002	Jean-Louis Ruelle	BM45351	2480

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EXAMINER	
BASKAR, PADMAVATHI	
ART UNIT	PAPER NUMBER
1645	4

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/889,267	Applicant(s) RUELLE, JEAN-LOUIS	
	Examiner Padmavathi v Baskar	Art Unit 1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25, 27, 29, 31, 32, 43- 44 and 46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25, 27, 29, 31, 43- 44 and 46* is/are rejected.

7)☒ Claim(s) *32* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

R spons to Amendment

1. Applicant's amendment filed on 6/6/03 is acknowledged. Claims 26, 28, 30, 33, 34, 35, 36 – 42, 45 and 47-49 have been canceled. Claims 25, 43 and 44 have been amended. Claims 25, 27, 29, 31, 32, 43, 44 and 46 are pending in the application.

2 The examiner acknowledges various amendments to the specification in response to the previous Office action.

3. Applicant is advised to amend the claims to restrict to SEQ.ID.NO: 2 since this is an elected invention, said election made in Paper # 8.

Rejections withdrawn

4. In view of amendment to the claims, the rejection under 35 U.S.C. 112, second paragraph is withdrawn. However, it is noted as to claims 25, 27, 29, 31, 32, 43- 44 and 46, the claim is indefinite as depending upon a non-elected claim or subject matter. Correction is required.

5. In view of amendment to the claims, the rejection under 35 U.S.C. 112, first paragraph is withdrawn for claims 43-44.

Rejections maintained

6. The rejection of claims 25, 27, 29, 31, 43- 44 and 46 under 35 U.5.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is referred to the interim guidelines on written description published June 15, 1998 in the Federal Register at Volume 63, Number 114, pp 32639-32645 (also available at www.uspto.gov). is maintained as set forth in the previous Office action.

The specification describes the polypeptide SEQ ID NO: 2, (see page 1-9) from Neisseria meningitidis comprising 722 amino acids. The actual biological function of the polypeptide, SEQ ID NO: 2 is not set forth in the specification. Applicants broadly describe the fragments of SEQ.ID.NO: 2 obtained by embracing any substitution, insertion or deletion of amino acid throughout the entire stretch of polypeptide by use of language in which a fragment sequence of 15 amino acids or 20 amino acids that matches an aligned contiguous segment of SEQ.ID.NO: 2. None of these fragments meets the written description provision of 35 U.S.C. 112, first paragraph. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that (he or she] invented what is claimed." (See Vas-Cath at page 1116.).

The specification fails to teach a single fragment of a polypeptide sequence of SEQ ID NO: 2 and it is noted that the claimed polypeptides do not exist as an invention independent of their function in a putative outer membrane polypeptide. The actual structure or other relevant identifying characteristics of each fragment having the claimed properties of the polypeptide can only be determined empirically by actually making every amino acid which can result in fragments with 15 or 20 amino acids and testing each to determine whether it is a polypeptide having the particularly disclosed properties of an BASB053 polypeptide.

There must be some nexus between the structure of the polypeptide fragments and the function of that fragment. The specification fails to teach the structure or relevant identifying characteristics of a representative number of species of a representative number of polypeptides, sufficient to allow one skilled in the art to determine that the inventor had possession of the invention as claimed. With the exception of an isolated polypeptide comprising SEQ ID NO: 2, fragments comprising 15 or 20 amino acids the skilled artisan cannot envision the contemplated sequences by the detailed chemical structure of the claimed fragments regardless of the complexity or simplicity of the art. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for making it. See Fiers v. Revel, 25 U5PQ2d 1601, 1606 (CAFC 1993) and Amgen Inc V Chugai Pharmaceutical Co Ltd., 18 U5PQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 U5PQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class.

Applicants' arguments filed on 6/12/03 have been fully considered but they are not deemed to be persuasive.

Applicant states that the disclosure of SEQ.ID.NO: 2 and the working examples found on pages 52-54 demonstrate that applicant was in possession of the invention as claimed.

The examiner disagrees with the applicant because neither the disclosure of SEQ.ID.NO: 2 nor the working examples found on pages 52-54 demonstrate that the applicant is in possession of the fragments of SEQ.ID.NO: 2 as these fragments have not been shown to

contain the particular properties of the full-length protein. For example: The immunogenic fragments that contain 15 or 20 contiguous amino acids induce an immune response. However, the immune response induced by these peptides would be able to recognize the full-length protein is not set forth in the claims. Therefore, this rejection is maintained.

7. The rejection of claims 25, 27, 29, 31, 43- 44 and 46 under 35 U.5.C. 112, first paragraph, because the specification, while being enabling for an isolated polypeptide comprising the amino acid sequence SEQ ID NO: 2 and a fusion protein comprising the amino acid sequence as set forth in SEQ.ID.NO: 2 and an heterologous amino acid sequence, the specification does not reasonably provide enablement for any immunogenic polypeptide comprising a fragment sequence of at least 15 or 20 amino acids that matches contiguous segment of SEQ.ID.NO: 2 or vaccines comprising SEQ ID NO: 2. is maintained as set forth in the previous office action.

(1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The specification fails to indicate the biological activity of SEQ ID NO: 2, fails to teach that SEQ ID NO: 2, a polypeptide that is detected by immune or convalescent sera and further lacks any description of polypeptide SEQ ID NO: 2 which acts as a vaccine comprising a fragment sequence of at least 15 or 20 amino acids that matches contiguous segment of SEQ.ID.NO: 2. The specification is not enabled for any immunogenic polypeptide comprising a fragment sequence of at least 15 or 20 amino acids that matches contiguous segment of SEQ.ID.NO: 2, because 1) the specification fails to teach that the alleged polypeptide SEQ ID NO: 2 is able to function as a vaccine 2) the specification fails to teach how to make and use fragments thereof that have an unknown and uncharacterized function; 3) the specification fails to teach what are the critical residues that can be modified and still achieve a fragment with any functional activity or any fragments with vaccine characteristics for Neisseria meningitidis, - 4) the art teaches that polypeptides with replacement of single amino acid residues may lead to both structural and functional changes in biological activity and immunological recognition, one skilled in the art would have reason to doubt the validity and functionality of the function of the polypeptide of SEQ ID NO:2 as a vaccine or use of fragments thereof and 5) applicants have not displayed a nexus between the structure of the amino acid sequence SEQ.ID.NO: 2 and function of the polypeptide as a vaccine.

As to points 1)- 5), the specification fails to provide a written description of any immunogenic polypeptide comprising a fragment sequence of at least 15 or 20 amino acids that

matches contiguous segment of SEQ.ID.NO: 2 or a polypeptide comprising the disclosed SEQ ID NO: 2 is able to be used as a vaccine. The specification fails to teach the critical polypeptide residues involved in the function of the polypeptide SEQ ID NO: 2, such that the skilled artisan is provided no guidance to test, screen or make fragments of the polypeptide comprising SEQ ID NO: 2 or the polypeptide comprising SEQ ID NO: 2, using conventional technology which allow for a vaccine use in the specification. The specification fails to teach to what extent one could alter SEQ ID NO: 2 and still present the sequence as a vaccine. The specification also fails to demonstrate the actual biological function of the polypeptide and only assigns it as a polypeptide. Even if one were to use the in vivo vaccine methodology of the specification to screen for a vaccine, one of skill in the art would be reduced to merely randomly altering amino acid(s), which would lead to unpredictable results regarding the functional activity of the polypeptide to be used as a vaccine. Moreover, polypeptide chemistry is probably one of the most unpredictable areas of biotechnology and the art teaches that the significance of any particular amino acid and sequences for different aspects of biological activity can not be predicted a priori and must be determined empirically on a case by case basis (Rudinger et al, in "PEPTIDE HORMONES", edited by Parsons, J.A., University Park Press, June 1976, page 6). The art specifically teaches that even a single amino acid change in a polypeptide leads to unpredictable changes in the biological activity of the polypeptide. For example, replacement of a single lysine residue at position 118 of the acidic fibroblast growth factor by glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological-activity of the polypeptide (Burgess et al., The Journal of Cell Biology, 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine, or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biologic activity of the mitogen (Lazar et al., Molecular and Cellular Biology, 8(3): 1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a polypeptide. Polypeptides with replacement of a single amino acid residue may lead to both structural and functional changes in biological activity and immunological recognition. For example, Jobling et al. (Mol. Microbiol. 1991, 5(7): 1755-67 teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis which products polypeptides that differ in native conformation, immunological recognition, binding and toxicity, thus exemplifying the importance of structural components to both biological function and immunological recognition. Applicants have not taught which residues of SEQ ID NO: 2 can be varied and still achieve a polypeptide that is functional as a vaccine. The specification has not conceived any other functionally equivalent polypeptide fragment and does not set forth the general tolerance to substitutions and where substitutions could be made. Since, the specification lacks a written description of any immunogenic polypeptide comprising a fragment sequence of at least 15 or 20 amino acids that matches contiguous segment of SEQ.ID.NO: 2 it is not enabled for this language because it fails to enable the skilled artisan to envision the detailed chemical structure of the claimed polypeptide fragments of SEQ ID NO: 2 as well as how to use the polypeptide fragments, one of skill in the art would be unable to produce these polypeptide fragments encompassed by the instant claims. Further, if one nucleotide is deleted or inserted at a single place within the coding sequence, all the codons down stream of that insertion or deletion will be frame shifted. The lack of enabling description of make and use a polypeptide comprising a fragment sequence of at least 15 or 20 amino acids that matches contiguous segment of SEQ.ID.NO: 2, the unpredictability associated with making and using the fragments of SEQ ID NO: 2 encompassed in the scope of the claims as set forth above, the lack of teaching even a beginning point for variation of the polypeptide sequence of SEQ ID NO: 2

for routine experimentation, lack of working examples commensurate in scope with the instant claims, the skilled artisan would be forced into undue experimentation to practice (i.e. make and use) the invention as is broadly claimed.

Applicants' arguments filed on 6/12/03 have been fully considered but they are not deemed to be persuasive.

Applicant submitted Exhibits A-D in order to support the scope of enablement for the rejected claims. The examiner has reviewed exhibit A, B, C, and D and specifically noted that Geyson (exhibit D) et al showed that antisera to the whole antigen was used to scan the specific peptide sequences. Thus, the peptides have been shown to contain functional activity. However, the claimed fragments have been shown to induce an antibody response but the immune response induced by these peptides would be able to recognize the full length protein is not set forth in the claims. Therefore, this rejection is maintained.

8. The rejection of claims 25, 27, 29, 31, 43- 44 and 46 under 35 U.S.C. 102(b) as being anticipated by Martin et al 1997 (J.Ex.Med. Volume 185, Number 7, April 7, 1997 1173-1184) as set forth in the previous office action.

Martin et al disclose an isolated polypeptide, outer membrane polypeptide from whole cell lysate of OM preparations from various clinical isolates including nine meningococcal strains two of serogroup A (604A and Z4063), one of serogroup B (608B [B: 2a:P1.2: L3]), two of serogroup C (2241C and 59C), one of serogroup 29-E, one of serogroup W-135, one of serogroup Y (SLATY) and one of serogroup Z (SLATZ) (page 1174, under materials and method, antigens). Monoclonal antibodies were produced by immunizing mice with OM preparation indicating that the disclosed isolated polypeptides are immunogenic and thus read on claim 46. Applicant's use of the open-ended term "comprising " in the claims fails to exclude unrecited steps or ingredients and leaves the claims open for inclusion of unspecified ingredients, even in major amounts. Whole cell lysates prepared in buffer (pharmaceutical carrier) from N.meningitidis inherently comprise the amino acid sequence as set forth in the SEQ.ID.NO: 2 and several N.meningitidis antigens. *See In re Horvitz, 168 F 2d 522, 78 U.S.P.Q. 79 (C.C.P.A. 1948) and Ex parte Davis et al., 80 U.S.P.Q. 448 (PTO d. App. 1948).* In the absence of evidence to the contrary the claimed isolated polypeptide comprising SEQ.ID.NO: 2 is inherent in the preparations of the disclosed prior art polypeptide. Since the Office does not have the facilities for examining and comparing applicants' claimed isolated polypeptide comprising SEQ.ID.NO: 2, with the polypeptide of prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product

of the prior art. *See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.*

Applicants' arguments filed on 6/12/03 have been fully considered but they are not deemed to be persuasive.

Applicant states that the recited prior art of record does not anticipate the claimed invention and cites MPEP 2131 for support. Applicant states that Martin et al do not disclose SEQ.ID.NO: 2 or less than SEQ.ID.NO: 2 immunogenic fragments.

It is the position of the Examiner that applicant failed to show that the disclosed cell lysates do not contain an isolated polypeptide comprising SEQ.ID.NO: 2. The examiner rejected the claims based on inherency since the cell lysates contain several proteins that include isolated polypeptide comprising SEQ.ID.NO: 2 and other *Neisseria* antigens.

The use of open-ended term "comprising in the claims fails to exclude unrecited steps or ingredients and leaves the claims open for inclusion of unspecified ingredients, even in major amounts See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Applicant's attention is drawn to claim 32. Claim 32 is not rejected because the claimed polypeptide comprises the amino acid sequence SEQ.ID.NO: 2.

9. Claims 32 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Status of Claims

10. Claims 25, 27, 29, 31, 43- 44 and 46 are rejected.

Claim 32 is objected.

Conclusion

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Padma Baskar whose telephone number is (703) 308-8886. The examiner can normally be reached on Monday through Friday from 6:30 AM to 4 PM EST

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Padma Baskar Ph.D.

9/16/03

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